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YOUNG & THOMPSON
209 Madison Street
Suite 500
ALEXANDRIA, VA 22314

EXAMINER	
STAPLES, MARK	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/547,669	CALISTRI ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/14/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-22* is/are pending in the application.

4a) Of the above claim(s) *7, 12, and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6, 8-11,13-19,21 and 22* is/are rejected.

7)☒ Claim(s) *1 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/20/2008 has been entered.

2. Applicant's amendment of claims 1 and 8 is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Applicant argues that the claim 13-21 should be rejoined. This is not persuasive for claim 20 as this claim recites a product, a kit which is not the elected group. The restriction requirement was made final in the action mailed on 03/28/2008. In so far as claim 13 has been amended to be in Group 1 and dependent claims 13-19 and 21 are within the original Group 1, they are examined in this action.

Applicant also is incorrect, in that claim 8 has only been examined as restricted to SEQ ID NOs: 9, 10, 13, 14, and 15. SEQ ID NOs. 11 and 12 have not been examined as they were not elected.

4. Claims 1, 2, 4-6, 8-11, 13-19, 21, and 22 are pending and at issue.

Declaration under 37 CFR 1.132 is insufficient

5. The Declaration under 37 CFR 1.132 filed 03/20/2008 is insufficient to overcome the rejection of claims 1, 2, 4-6, 8-11, and 22 based upon Shuber (2001) under 35 U.S.C. 102(b), further in view of Zhou et al. (2002) under 35 U.S.C. 103(a), and further in view of Kmiec et al. (2001), Kmiec et al. and Albertsen et al. (2001), and Buck et al. (1999) under 35 U.S.C. 103(a) as set forth in the last Office action because: the declaration does not clearly identify the singular "the primer" which was used to generate the test results (see Declaration, page 5, 1st sentence under the section *Fluorescence long DNA (FL-DNA) analysis*).

Hence, it is not possible for Examiner to determine how the results of the Declaration relate to the broadly claimed "primers" (plural, as recited in claim 1 line 7) or to any specifically claimed primer, including primers of SEQ ID NOs: 9-16 (as recited in claim 8). Additionally the primers used for comparison to the claimed method are not identified.

Furthermore there is no recitation in at least claims 1, 4-6, 9-11, and 22 of a use of the primers which is not taught in the prior art methods of Shuber (2001).

Furthermore, the Declaration does not provide how presence of a tumor in a subject was known, independent of the claimed methods with the claimed primers and independent of the comparison method with "new" primers. Also the amount of starting sample was different between the claimed method and the comparison method and it is uncertain whether the amount of starting material, even with normalizing the results, is a confounding factor which affects sensitivity and/or specificity.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Objection and Rejection that are Withdrawn

Objection Withdrawn

6. The objection to the claim 22 as not being further limiting is withdrawn in light of Applicant's amendment of claim 1 which subsequently makes claim22 further limiting.

Claim Rejection Withdrawn - 35 USC § 112 Second Paragraph

7. The rejection of claims 1, 2, 4-6, 8-11, and 22 under 35 USC § 112 Second Paragraph is withdrawn in light of Applicant's amendment of claim 1 to recite a step for determining the presence of pre-cancerous lesions.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 102(b)

8. The rejection of claims 1, 4-6, 9-11, and 22 under 35 U.S.C. 102(b) as being as being anticipated by Shuber (WO 2001/42502) is maintained

Applicant's arguments filed 03/14/2008 have been fully considered but they are not persuasive.

Applicant agrees that Shuber teaches fluorescent labels but argues that Shuber does not teach using the fluoresecent labels in a method of amplifying of the instant

claims. Examiner disagrees as Shuber specifically states: "The amount of amplification product may be determined by any suitable or convenient means. . . . Labels, such as fluorescent or radioactive labels, may be used" (see 1st and 3rd sentences of the 2nd paragraph on p. 8). Applicant also argues that Shuber teaches other methods of detection such as gel electrophoresis and ethidium bromide staining. Regardless of this, Shuber teaches the recited fluorescent methods of detection.

Applicant further argues that Shuber teaches PCR amplification. First, Shuber teaches general amplification as already noted. Second, PCR amplification is not precluded as a method of amplification in the instant claims. Applicant continues in argument to assert that ethidium bromide staining methods are less sensitive than fluorescent methods. However, this argument is off point as whatever else Shuber may teach, Shuber teaches the fluorescent methods of the instant claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the best cut-off to discriminate between healthy subjects and patients) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As Shuber teaches the steps and elements of the instant claims, the teachings of Schuber anticipate the instant claims and the rejections are maintained.

Claim Rejections Maintained - 35 USC § 103

9. The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) and further in view of Zhou et al. (2002) is maintained.

Applicant's arguments filed 03/14/2008 have been fully considered but they are not persuasive. Applicant argues that Zhou et al. do not teach the steps of the instant claims. However and as noted above, Shuber is relied upon for these teachings.

10. The rejection of claim 8 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) and further in view of Kmiec et al. (W0 2001/73002), Kmiec et al. and Albertsen et al. (2001), and Buck et al. (1999) is maintained.

Applicant's arguments filed 03/14/2008 have been fully considered but they are not persuasive. Applicant argues that the claimed primers do not simply represent structural homologs of the cited prior art. However Applicant presents no evidence that the claimed primers have any structural feature which is not found or is not obvious in view of the prior art. The exact same nucleic acid sequences are disclosed in the prior art, as given in the prior Office action. Buck et al. teach that it is obvious to prepare primers from any known nucleic acid sequence. The fluoresent modification to the sequences is anticipated by the teachings of Shuber and the use of fluorescein is obvious as taught by Zhou et al.

Applicant further argues that Buck et al. do not teach the quantification of DNA as recited in the instant claims. However, Buck et al. are not relied upon for this teaching, Shuber is relied upon for this teaching as given previously.

Applicant then argues the data of Tables 1, 2a, and 2b indicate that primers of the instant claims produce results indicative of a different ability to discriminate between cancer patients and healthy subjects. As already noted in regard to the Declaration concerning these tables, Examiner is unable to determine what primers were used to generate the data in these tables and hence is unable to determine if any of these primers are those of the instant claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., fluorescence Long DNA analysis) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

New Rejections

Claim Objections

11. Claims 1 and 13 are objected to because of the following informalities: improper grammar in reciting "with fluorescent molecule". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 2, 4-6, 8-11, 13-19, 21, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1, 2, 4-6, 8-10, 13-19, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the reference value is determined.

14. The term "pre-cancerous lesion" in claims 1 and 13 is a relative term which renders the claim indefinite. The term "pre-cancerous lesion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Dependent claims 2, 4-6, 8-11, 14-19, 21 and 22 are thus also indefinite. That the term "pre-cancerous lesion" is indefinite is evidence by Srivastava et al. (1999) who teach:

> "Terms such as . . . 'pre-cancerous' . . . are often encountered in cancer research, but their precise meaning is often ill-defined and can be interpreted variably" (see Introduction on p. 13)
> and
> "The term 'precancer' is ambiguous . . ." see next to last sentence of 2nd paragraph on p. 13).

Thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

15. Claims 11 and 19 recites the limitation "lesions" in 4. There is insufficient antecedent basis for this limitation in the claim. It is noted that the there is antecedent

basis for the term "pre-cancerous lesions" respectively in claims 1 and 13, but not for the broader term which is "lesions".

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 13, 15-19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001), Kmiec et al. (W0 2001/73002, previously cited), Kmiec et al. and Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited).

Regarding claims 13, 16, and 21, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:
a) extracting DNA from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");
b) PCR amplifying at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labelled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA, the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification

reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2);

c) quantifying the amplified fragments (amplicons);

d) calulating the total amount of different amplicons;

e) comparing the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as "Q#", which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the "NEG CONTROL" as a reference value, and in Figures 1-7 is also compared to the "POSITIVE CONTROL" as another reference value). Shuber further teaches that a total amount of amplicons, that is amplifiable nucleic acid, is indicative of disease by teaching: "As shown in those figures [11A and 11B], patients with [colorectal] cancer or adenoma have an increased yield of amplifiable DNA." (see p. 22 lines 20 and 21).

Further regarding claim 13, Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 1 of Office Action mailed on 03/28/2008).

Regarding claims 15 and 17, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight, as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catnenin, mlh-1 , pms-l , pms-2, pol-delta, and bax").

Regarding claim 18, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to . . . machine-driven optical comparison, densitometry, . . . and other known means").

Regarding claim 19, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: "Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient"; and see p. 10, 2nd paragraph, 3rd sentence: "A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples").

Shuber does not teach other elected sequences of instant claim 13 or sequences comprising these.

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 1 of Office Action mailed on 03/28/2007).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 1 of Office Action mailed on 03/28/2007).

Albertsen et al. do not teach SEQ ID NOs: 9, 10, 13, 14, or 16; or sequences comprising these.

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 13 is rejected for SEQ ID NOs: 9, 10, 13, 14, 15, and 16, as described following. With regard to Claim 13, for primers designed for amplification of APC gene, Shuber, Kmeic et al. and Alberston et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 9, 10, 13, 14, 15, and 16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 9, 10, 13, 14, 15, and 16 are contained within the sequences disclosed by Shuber, Kmeic et al. and Alberston et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 9, 10, 13, 14, 15, and 16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of

extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

17. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001), Kmiec et al. (W0 2001/73002, previously cited), Kmiec et al. and Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited) as applied to claim 13 above, and further in view of Zhou et al. (2002).

Shuber teaches as noted above.

Shuber does not specifically teach fluorescein as a fluorescent label.

Regarding claim 14, Zhou et al. teach the fluorescent label fluorescein (see 7th sentence of the section *Principles of digital SNP analysis* on p. 359).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber by using the fluorescent label fluorescein as suggested by Zhou et al. with a reasonable expectation of success. The motivation to do so is provided by Zhou et al. who teach that mutations in alleles associated with colorectal tumors can be detected with fluorescein as a label (entire article, especially the section *Principles of digital SNP analysis* on p. 359). Thus,

the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

18. No claim is free of the prior art.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
July 17, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637